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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

David E. Comings

Serial No.: 09/825,922

Filed: 5 April 2001



Group Art Unit: 1614

Examiner: Not yet assigned

For: METHOD OF PROFILING GENES  
AS RISK FACTORS FOR  
ATTENTION DEFICIT  
HYPERACTIVITY DISORDER

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents  
Washington, DC 20231

Dear Sir:

Prior to examination of the above identified application, please make the amendments shown on the following pages. A marked-up copy of the amendments with inserted material underlined and deleted material within square brackets is attached to this preliminary amendment.

09825922-070601

IN THE SPECIFICATION:**Clean Copy of Page 3, Paragraph on Lines 29-30**

Figures 1A-1 through 1A-3 and 1B-1 through 1B-5 describe the ANOVA of ADHD scores for the genotypes of forty genes.

**Clean Copy of Page 4, Paragraph on Lines 3-5**

Figures 3A-C summarize the results for individual genes that were included in the regression equation after all forty-two genes were entered as independent variables and the nonsignificant ones removed by backward elimination.

**Clean Copy of Page 10, Paragraph on Lines 9-23**

**Polymorphisms.** The polymorphisms for the first 20 dopamine, serotonin, and norepinephrine genes are provided herein (see Figures 1A-1 through 1A-3). Figures 1B-1 through 1B-5 describe 22 additional genes, their associated polymorphisms, the results of ANOVA comparing the mean ADHD, ODD and CD scores for the three genotypes, and the resultant gene score based on the ANOVA results. See *Scoring of the Genes (supra)* for the rationale for the gene scoring and other aspects of the technique. Each gene were scored 0 to 2 based on either prior results in the literature (literature references are set forth in Comings et al., 2000c) about which genotypes were associated with the given phenotype, or based on ANOVA for the three genotypes (11, 12 and 22) on the same subjects used for the multivariate regression analysis. We have termed the latter 'optimized' gene scoring and it is used when there is no prior literature for a given gene or a given phenotype. Since all genes are optimized in the same fashion, this allows a comparison of the relative effect of the genes examined. The genes scores in Figures 1B-1 through 1B-5 are optimized genes scores. Since virtually none of these have previously been examined in ADHD, ODD or CD, no literature-based genes scores were available. The following polymorphisms have been developed in our own laboratory and have not been previously published.

**Clean Copy of Page 11, Paragraph on Line 30 through Page 12, Line 3**

Figures 1B-1 through 1B-5 list the results of ANOVA using the continuous traits for ADHD, ODD or CD as the dependent variables and the three genotypes of the 22 additional genes as the independent variables. These results determine how the genes will be scored for the regression analysis. The gene scores for the 22 additional genes plus the 20 earlier described genes were then entered into the regression analysis as independent variables.

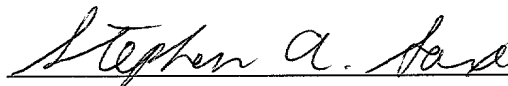
**Clean copy of Page 12, Paragraph on Lines 3-11**

Figure 2 presents the results for ADHD, ODD, and CD for all 42 genes. The diagram shows the genes and functional groups of genes that were included in the equation, the fraction of the variance ( $r^2$ ) contributed, and the p values that were  $< .05$ . Figure 2 presents the sum of the  $r^2$  values for the eight functional groups of genes, based on simply adding the individual  $r^2$  values from Figures 1A-1 through 1A-3 and 1B-1 through 1B-5. The p values were based on performing an individual multivariate regression analysis on a given functional group of genes. The p values of those groups that were significant are given. Figure 2 presents the final  $r$ ,  $r^2$ , adjusted  $r^2$ , F, p values, and the number of genes included for ADHD, ODD, and CD, for the 42 genes examined.

REMARKS

This Preliminary Amendment is submitted concurrently with formal drawings. The formal drawings have been modified slightly in comparison with the informal drawings which were submitted with the application. The modifications were required to make the drawings conform to the requirements for drawings. The amendments made to the specification by this Preliminary Amendment are solely to make the specification conform to the numbering of the formal drawings which differs slightly from the numbering of the informal drawings. It is urged that no new matter is presented and it is requested that these amendments be entered.

Respectfully submitted,



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**Amended Page 3, Paragraph on Lines 29-30: Version with markings to show changes made**

Figures [1(a) and (b)] 1A-1 through 1A-3 and 1B-1 through 1B-5 describe the ANOVA of ADHD scores for the genotypes of forty genes.

**Amended Page 4, Paragraph on Lines 3-5: Version with markings to show changes made**

[Figure 3 summarizes] Figures 3A-C summarize the results for individual genes that were included in the regression equation after all forty-two genes were entered as independent variables and the nonsignificant ones removed by backward elimination.

**Amended Page 10, Paragraph on Lines 9-23: Version with markings to show changes made**

**Polymorphisms.** The polymorphisms for the first 20 dopamine, serotonin, and norepinephrine genes are provided herein (see [Figure 1a] Figures 1A-1 through 1A-3). [Figure 1b describes] Figures 1B-1 through 1B-5 describe 22 additional genes, their associated polymorphisms, the results of ANOVA comparing the mean ADHD, ODD and CD scores for the three genotypes, and the resultant gene score based on the ANOVA results. See *Scoring of the Genes (supra)* for the rationale for the gene scoring and other aspects of the technique. Each gene were scored 0 to 2 based on either prior results in the literature (literature references are set forth in Comings et al., 2000c) about which genotypes were associated with the given phenotype, or based on ANOVA for the three genotypes (11, 12 and 22) on the same subjects used for the multivariate regression analysis. We have termed the latter 'optimized' gene scoring and it is used when there is no prior literature for a given gene or a given phenotype. Since all genes are optimized in the same fashion, this allows a comparison of the relative effect of the genes examined. The genes scores in [Figure 1b] Figures 1B-1 through 1B-5 are optimized genes scores. Since virtually none of these have previously been examined in ADHD, ODD or CD, no literature-based genes scores were available. The following polymorphisms have been developed in our own laboratory and have not been previously published.

**Amended Page 11, Paragraph on Line 30 through Page 12, Line 3: Version with markings to show changes made**

[Figure 1(b) lists] Figures 1B-1 through 1B-5 list the results of ANOVA using the continuous traits for ADHD, ODD or CD as the dependent variables and the three genotypes of the 22 additional genes as the independent variables. These results determine how the genes will be scored for the regression analysis. The gene scores for the 22 additional genes plus the 20 earlier described genes were then entered into the regression analysis as independent variables.

**Amended Page 12, Paragraph on Lines 3-11: Version with markings to show changes made**

Figure 2 presents the results for ADHD, ODD, and CD for all 42 genes. The diagram shows the genes and functional groups of genes that were included in the equation, the fraction of the variance ( $r^2$ ) contributed, and the p values that were  $< .05$ . Figure 2 presents the sum of the  $r^2$  values for the eight functional groups of genes, based on simply adding the individual  $r^2$  values from Figures [1a] 1A-1 through 1A-3 and [1b] 1B-1 through 1B-5. The p values were based on performing an individual multivariate regression analysis on a given functional group of genes. The p values of those groups that were significant are given. Figure 2 presents the final  $r$ ,  $r^2$ , adjusted  $r^2$ , F, p values, and the number of genes included for ADHD, ODD, and CD, for the 42 genes examined.